Development of Portable Device for Monitoring the Lithium Level from Bipolar Disorder Patients.

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Abstract— **This research aims at developing low cost portable proactive healthcare technologies to put more control into the hands of patients especially who have mental illness so that the earliest signs of health problems with medications can be detected and corrected. Monitoring prescription drugs such as lithium, clozapine etc is important for safe guarding the well-being of the bipolar sufferers. Therapeutically useful amounts of lithium (~ 0.6 to 1.2 mmol/L) are only slightly lower than toxic amounts (>1.5 mmol/L), so the concentration of lithium must be carefully monitored during treatment to avoid toxicity. A very sensitive analytical method was proposed for the spectrofluorimetric determination of lithium base on its reaction with 1,4-dihydroxyanthraquinone (Quinizarin). The fluorescence is measured at an excitation wavelength of 590 nm and emission wavelength of 620 nm. Saliva sample was tested using the proposed portable device in order to validate the feasibility of saliva as a sample to detect lithium ions. Calibration results presented that linear range of detection was 0.25 mM ~ 6.0 mM of Li^+ in saliva with R^2=0.99. The range of detection covers sufficiently the therapeutic range of lithium drugs.**

Keywords-component; bipolar disorder; lithium; fluorescence; portable device

I. INTRODUCTION

According to the American Psychiatric Association (APA) guidelines for treating bipolar disorder, atypical medication for bipolar patients with severe mania or mixed episodes is an antipsychotic medication combined with mood stabilizers, anti-manic/depressant agents [1].

Lithium (brand names Eskalith, Lithobid, Lithonate, and Lithotabs) is the most widely used and studied medication for treating bipolar disorder. Lithium helps reduce the severity and frequency of mania. It may also help relieve bipolar depression [2-4]. Although lithium is highly effective at reducing the frequency and intensity of mood swings, it is also a very difficult and potentially dangerous drug for patients. Therapeutically useful amounts of lithium (~ 0.6 to 1.2 mmol/L) are only slightly lower than toxic amounts (>1.5 mmol/L), so the concentration of lithium must be carefully monitored during treatment to avoid toxicity [5]. Also, it is necessary to maintain steady lithium concentration to keep the patient in stable mood. Since lithium's therapeutic dose is uncomfortably close to its toxic dose, meaning it is rather easy to take too much lithium by mistake and become poisoned. Toxically high blood lithium levels can cause respiratory depression, seizures, coma and even death. The monitoring of lithium level for bipolar disorder patients is clearly an important aspect of treatment as the side effects (polyuria, polydipsia, weight gain, cognitive problems, sedation or lethargy) of treatment risks to thyroid and kidney can be reduced or eliminated by dose adjustment or dosage schedule [5,6]. Therefore, patients need to have regular tests to monitor the levels of lithium based medication.

Saliva has been considered as an alternative matrix for biochemical parameter monitoring. Human saliva is 98% water, but it contains many important substances, including electrolytes, mucus, antibacterial compounds and various enzymes. It has been used to assess a variety of disease activities and the levels of certain drugs and hormones [7,8]. Saliva collection is non-invasive and less stressful when compared to blood collection.

This paper presents part of our work in developing a low cost, non-invasive portable healthcare technology to put more control into the hands of patients so that the earliest signs of problems can be detected and corrected by monitoring the drug level from the saliva. Here, a very sensitive analytical method was investigated for the spectrofluorimetric determination of lithium base on its reaction with 1,4-dihydroxyanthraquinone (Quinizarin) [9,10]. The fluorescence is measured at 620 nm with an excitation wavelength of 590 nm.

II. EXPERIMENTAL

A. Experimental setup

A portable biochemical device was developed to measure the intensity of fluorescence. The light source (λmax: 590nm, 50mW) and photo detector (OPT101: Texas Instruments) were configured at 90 degree angle in the opaque cuvette holder as shown in Fig. 1. The photo detector was covered by a red band pass filter to detect emission light at 620nm. Digital output voltage signal from the photo detector was achieved with an 8 bits micro-controller (PIC12F675, Microchip Technology Inc.) and the data were logged and time stamped.

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B. Preparation of reagents and standards

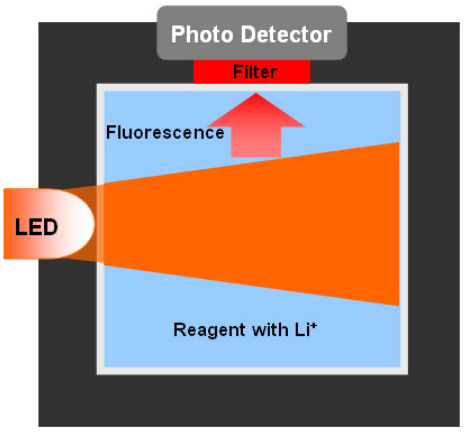

Figure 1. Schematic of the optical sensing module for the measurement of fluorescece.

Analytical grade reagents were used for all experiments and aqueous solutions were prepared using de-ionized water. For the calibration, 50mM stock lithium solution was prepared by dissolving LiCl (Sigma Aldrich) in water. Standard solutions of lithium were prepared by diluting the stock solution. 35mM NaOH was prepared in water. The fluorescent dye solution was prepared by dissolving 1,4-dihydroxy-anthraquinone (Sigma Aldrich) in dimethylsulfoxide (Sigma Aldrich) to make 15µM stock.

C. Calibration process for aqueous sample

1mL of 15uM quinizarin in dimethylsulfoxide solution was added into a standard quartz or disposable cuvette; followed by 50µl of 0.035M NaOH solution. Then 10µL of Li^+ sample was spiked into prepared reagent. The mixture was thoroughly stirred before read by the spectrofluorimeter and/or the portable device to measure the intensity of fluorescence.

D. Calibration process for saliva sample

Saliva sample was collected from a healthy volunteer. The oral cavity was thoroughly rinsed with water about 5 minutes before to collect newly produced saliva sample. Unstimulated saliva was collected mainly from sublingual glands located under the tongue using dripping method where saliva was allow to drip into a propylene vial. 1-3 mL of sample was collected each time.

Doped saliva sample was prepared by mixing 35µL of saliva sample with 5µL of Li^+ solution with known concentration. The doped saliva was added into 1mL of 15uM quinizarin in DMSO with 8µL of 0.28M NaOH. After mixing the sample and reagent, the fluorescence was measured by spectrofluorimeter and the in-house developed portable device.

III. RESULTS

Excitation and emission spectra scan was performed to investigate the optimal wave length for the detection of lithium. and scanned results showed in Fig. 2. Two major excitation

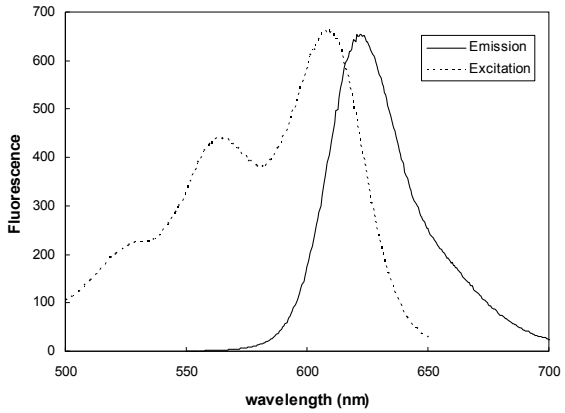

Figure 2. The excitation scan and emission scan of 15µM quinizarin in the presence of 25µM lithium.

peaks were found at 565nm and 610nm. Emission peak was found at 624nm. Ideally excitation at 610nm should be used to give stronger fluorescence intensity but due to the difficulty in filtering out the excitation wave length, LED with peak emission at 590nm was selected as excitation light source.

The optimization of reagent was performed in order to increase the sensitivity and stability of proposed spectrofluorimetric method. The result of optimization presented in Fig. 3 that the highest intensity of fluorescence was measured with the concentration of 15µM quinizarin in DMSO. Higher concentration of quinizarin did not give more emission due to re-absorption of emission light by the dye. 40µM of NaOH was used as insufficient amount of NaOH caused fluorescence instability.

The calibration (3 repeats) was performed with aqueous Li^+ standards. The calibration curve is linear over the concentration ranges of 0 – 40µM of Lithium ion with R^2=0.996 as shown in Fig. 4. In comparison with standard spectrofluorimeter, the linearity range of portable device showed superior performance with much lower detection limit, hence it is an excellent

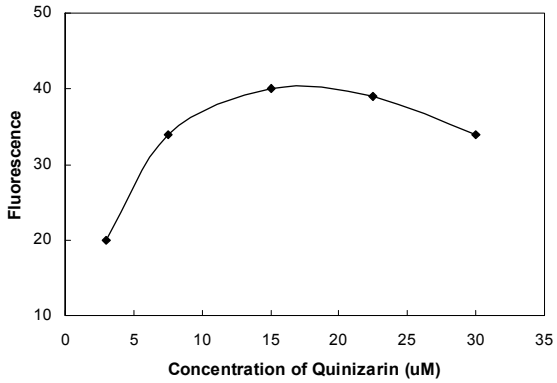

Figure 3. Optimization of dye (quinizarin) concentration in DMSO.

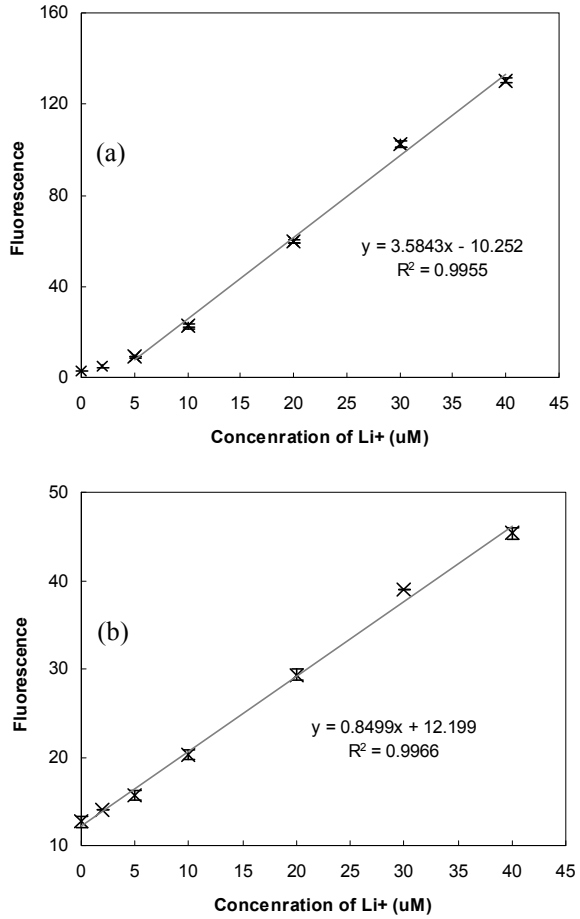

Figure 4. Validation of developed portable device with spectro-fluorimeter. The measurement of fluorescece using (a) spectrofluorimeter (b) portable device.

sensing device for lithium ions detection.

Saliva sample was tested using portable device in order to validate the feasibility of saliva as a sample to detect lithium ions. According to the clinical tests, the salivary lithium concentration is 2.2 ~ 2.5 times higher than serum lithium with significant correlation factor [11-13]. Unstimulated saliva was collected and known concentration of Li^+ was spiked into the saliva to prepare the Li^+ doped saliva. Using lithium doped salivary sample, calibration was performed. Results presented in Fig. 5 show calibrations obtained from different saliva samples collected on different days. Similar results were obtained with linear range of detection between 0.25mM ~ 6.0 mM of Li^+ and R^2=0.990. When we consider the therapeutic range of lithium in serum is 0.6 ~ 1.0 mM, the expected salivary lithium concentration would be higher than lithium in serum. Linear range of the proposed method covers sufficiently the therapeutic range of lithium drugs.

IV. CONCLUSIONS

Saliva sample was tested using portable device in order to validate the feasibility of saliva as a sample to detect lithium ions. Calibration results presented that the linear range of detection was 0.25 ~ 6.0 mM of Li^+ in saliva with R^2=0.990. The range of detection offered by the portable device covers sufficiently the therapeutic range of lithium. This rapid and simple way of lithium measurement will help to monitor and thus maintain a steady lithium concentration.

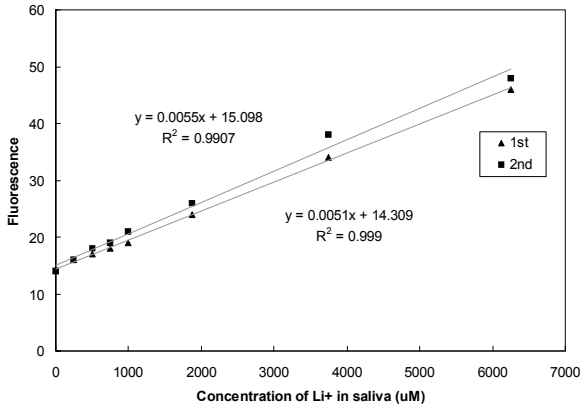

Figure 5. Calibration results from Li^+ doped saliva with portable device.

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